REMARKS

Claims 1, 2, and 4-9 are pending in the instant application. Claims 1, 2, and 4-9 have been rejected. Claim 1 has been amended. Claim 2 has been canceled. No new matter has been added by this amendment. Reconsideration is respectfully requested in light of the following remarks.

I. Withdrawn Rejections

Applicants are pleased to acknowledge that the rejections based on enablement under 35 U.S.C. §112, first paragraph and 35 U.S.C. §102(a) and (b) have been withdrawn.

II. Rejection of Claims Under 35 U.S.C. §112

Claims 1, 2 and 4-9 have been rejected under U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In particular, the Examiner suggests that the claims are drawn to a genus of polypeptides including modified polypeptide sequences, that have not been disclosed in the specification. It is suggested that no information beyond the characterization of the function (β-glucuronidase and it repressor, hormone binding domain) of a single species was provided by the specification to indicate that Applicants were in possession of the claimed genus of modified polypeptides. The Examiner suggests that the specification does not provide a structure and function of all the polypeptide sequences, including fragments and variants,

within the scope of the claimed genus. It is suggested that the genus of polypeptides claimed is a large variable genus including peptides which can have a wide variety of functions and with the potentiality of generating many different antibodies and therefore, many structurally and functionally unrelated polypeptides are encompassed within the scope of the claims.

Applicants respectfully traverse this rejection.

MPEP 2163 indicates that compliance with the written description requirement of 35 U.S.C. §112, first paragraph, may be shown by any description of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, *i.e.*, complete or partial structure, other physical and/or chemical properties, *functional characteristics when coupled with a known or disclosed correlation between function and structure*, or some combination of such characteristics.

Accordingly, in an effort to facilitate the prosecution of this application, Applicants have amended claim 1 to recite the identifying combination of characteristics of the various components of the chimeric protein used for detecting the presence or activity of a pre-determined protease. In view of these amendments, claim 2 has been canceled. Specifically, a cellular repressor domain of the chimeric protein of the invention must meet the criteria of: a) being obtained from a steroid hormone receptor or a bHLH/PAS transcription regulator, and b) repress activity of a normally biologically active protein fused thereto (see page 9, line 25 to page 10, line 28 in support of this amendment). Further, a reporter domain of the chimeric protein of the invention must meet the criteria of: a) having a

detectable biological activity when not fused to the repressor domain, and b) comprise a β-glucuronidase (see paragraph bridging page 10 and 11). Moreover, a protease cleavage domain linking the repressor domain to the reporter domain must have a structure that is cleaved by activity of a pre-determined protease (see Table bridging page 11 and 12). Thus, using these identifying characteristics along with the art-established correlation between function and structure, one of ordinary skill in the art could recognize Applicants were in possession of the claimed invention.

MPEP 2163 states that "[w]hat is conventional or well known to one of ordinary skill in the art need not be disclosed in detail." See *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d at 1384, 231 USPQ at 94. At the time of filing, the structure of repressor domains obtained from steroid hormone receptors was well-established (see, *e.g.*, Mattioni et al. (1994) *Meth. Cell Biol.* page 343, Table III) and it was well-known in the art that the PAS domain (a helix-loop-helix structure) of the bHLH/PAS superfamily of transcription regulators harbors a repressor domain (see page 10, lines 15-21 of the instant application). Moreover, wild-type and biologically functional variants of β-glucuronidase isolated from various species are well-known in the art and as acknowledged by the Examiner the use of β-glucuronidase as a reporter enzyme has been documented in the art from a very long time ago. Further, the specification provides a detailed description of suitable protease cleavage sites and their corresponding pre-determined proteases (see Table bridging page 11 and 12). Therefore, a skilled artisan would have understood that Applicants were in possession of the claimed

invention at the time of filing, even if every nuance of the claims were not explicitly described in the specification, as the structural and functional relationship of the repressor domains of the claimed cellular receptors, reporter domain of a β-glucuronidase, and protease cleavage sites of pre-determined proteases were taught in the specification or established in the art. Accordingly, withdrawal of this rejection is respectfully requested.

III. Rejection of Claims Under 35 U.S.C. §103

Claims 1, 2, 4-5 and 9 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Xu et al. ((1998) *Nucleic Acids Res.* 26:2034-2035), Mattioni et al. ((1994) *Meth. Cell Biol.* 43:335-352) and Hull et al. ((1995) *Meth. Mol. Biol.* 49:125-141).

The Examiner suggests that Xu et al. teach in general the use of chimeric proteins comprising a repressor domain which represses the activity of a normally biologically active protein fused thereto as a reporter domain having a detectable activity when not fused to the repressor domain, both of which are linked together through a linking sequence comprising a protease cleavage domain of the predetermined protease, wherein the protease cleavage domain comprises a cleavage site for a caspase, wherein the linker sequence comprises spacers in between the repressor or reporter and protease cleavage site.

It is suggested the Hull et al. provide extensive information regarding the use of β-glucuronidase as reporter and that it is clear to those skilled in the art that the use of β-glucuronidase in reporter systems was well-known in the art and

that said enzyme was most favored for developing a reporter system.

The Examiner further suggests that Mattioni et al. teach regulation of protein activities by fusion to steroid binding domains and that an alternate method to inducible expression of a protein activity can be developed by making a fusion protein, comprising the protein of interest whose activity needs to be controlled (*i.e.*, reporter domain) and a HBD sequence linked to the N-terminal or C-terminal of the reporter protein wherein steric hinderance created by the HBD renders the reporter inactive.

The Examiner further suggests that with these references in hand it would have been obvious to one of ordinary skill in the art to combine the teachings and arrive at a fusion protein as recited by claims 1-2, 4-5 and 9 because it would have been obvious to those skilled in the art to replace the repressor and the reporter taught by Xu et al. with the β-glucuronidase and its repressor and construct a fusion protein comprising a reporter such as β-glucuronidase and the HBD such as the GR-HBD linked through a predetermined protease cleavage site such as that of a specific caspase and use it to determine the presence of said protease. It is further suggested that one would have been motivated to do so in order to develop an alternate system to that developed by Xu et al., *i.e.*, an enzyme-based fusion protein and assay as opposed to the fluorescent protein-based fusion protein and assay as developed by Xu et al. The Examiner suggests that one of ordinary skill in the art would have had a reasonable expectation of success since the above references teach all the important aspects of the invention.

Applicants respectfully traverse this rejection.

MPEP § 2141 states that when applying 35 U.S.C. 103, the following tenets of patent law must be adhered to: (A) The claimed invention must be considered as a whole; (B) The references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination; (C) The references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention; and (D) Reasonable expectation of success is the standard with which obviousness is determined. *Hodosh v. Block Drug Co., Inc.*, 786 F.2d 1136, 1143 n.5, 229 USPQ 182, 187 n.5 (Fed. Cir. 1986).

Applicants respectfully disagree with the Examiner. When considered as a whole, the claimed invention combines a cellular receptor repressor domain and a β-glucuronidase reporter protein, joined by a protease cleavage site. When the repressor domain and reporter protein are in close proximity, the reporter protein is inactive. Upon protease cleavage of the protease cleavage site, the repressor domain and reporter protein are physically separated and biological activity is detectable.

In contrast, the assay taught by Xu et al. operates on the exact opposite principle. Activity of the acceptor reporter protein is only detected when the donor protein is in close proximity so that electrons can be transferred between the donor and acceptor proteins. Upon cleavage by a protease, the donor and acceptor are physically separated and no biological activity is detectable. Moreover, while EGFP and BGFP are reporter proteins, Xu et al. does not teach a cellular receptor repressor domain which represses activity of a normally biologically active protein fused thereto in combination with a reporter protein. In

fact, when considered as a whole, Xu et al. actually teach away from the desirability of generating an alternate method such as the instant invention in stressing that the major advantage of using the fluorescent protein-based assay is that no cell staining is needed and live cells can be monitored continuously during the course of the experiment (see page 2035, column 1, ¶2). Thus, in view of such an advantage, the skilled artisan would have little motivation to modify the teachings of Xu et al. and substitute EGFP or EBFP with the β-glucuronidase of Hull et al. and take the additional step of using a cellular receptor repressor domain of Mattioni et al. to inactivate said reporter as the assay of Xu et al results in the loss of detectable activity of the reporter and the assay of the present invention results in the gain of detectable activity of the reporter when a pre-determined protease is present. Only the hindsight vision afforded by the claimed invention would motivate the skilled practitioner to combine the cited references and arrive at the instant invention. It is therefore respectfully requested that this rejection be withdrawn.

Claims 6-8 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Xu et al. ((1998) *Nucleic Acids Res.* 26:2034-2035), Mattioni et al. ((1994) *Meth. Cell Biol.* 43:335-352) and Hull et al. ((1995) *Meth. Mol. Biol.* 49:125-141) as applied to claims 1-2, 4-5 and 9 and further in view of the common knowledge in the art.

The Examiner suggests that using the teachings of Xu et al., Mattioni et al. and Hull et al. it would have been obvious to those skilled in the art to have multiple reporter domains such that the signal intensity obtained from the reporter domain,

whether via fluorescence as in Xu et al. or the activity of the reporter enzyme as in the instant case would be more intense and its detection be easier. The Examiner further suggests that because of the simplicity and ease of use of the technique it would have been obvious to one of skill in the art to use multiple protease cleavage sites and detect the presence of multiple sets of proteases. The Examiner indicates that one of skill in the art would have been motivated to do so in order to develop intense signal during the assay.

Applicants respectfully traverse this rejection.

Applicants respectfully disagree with the Examiner's suggestion that claims 6-8 are obvious in light of the teachings of Xu et al., Mattioni et al. and Hull et al. for the reasons set forth above in that these references fail to teach, suggest, or motivate the skilled artisan to combine the teachings of the cited references to arrive at the instant inventive chimeric protein of claim 1. Accordingly, as set forth in MPEP §2143.03, when an independent claim is nonobvious under 35 U.S.C. §103, then any claim depending therefrom is nonobvious. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988). Thus, withdrawal of the rejection of claims 6-8 is respectfully requested.

IV. Conclusion

The Applicants believe that the foregoing comprises a full and complete response to the Office Action of record.

Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,

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